

Review of common cutaneous adverse drug reactions

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Introduction

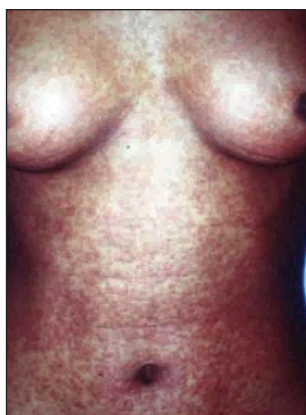
Cutaneous adverse drug reactions are amongst common conditions seen in Dermatology. An adverse drug reaction may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side-effects and unanticipated adverse manifestations. Adverse drug reactions may be said to be the inevitable price we pay for the benefits of modern drug therapy. Some drug reactions cause minor symptoms to patients whilst others are life threatening, thus they are costly both in terms of the human illness caused and in economic terms, and can undermine the doctor-patient relationship. In this article I am briefly discussing common cutaneous drug reactions.

1. Exanthematic (maculopapular) reaction

This is by far the commonest form of cutaneous reaction to a drug.¹ It may develop within hours to days after drug administration, and may be accompanied by fever, pruritus and eosinophilia. The clinical features are variable, the lesions may be scarlatiniform, rubelliform or morbilliform, or may consist of a diffuse eruption of erythematous macules and papules (Figure 1). The distribution is variable, but it is generally symmetrical, occurring commonly on the trunk and extremities. Any drug can cause this kind of cutaneous reaction. Treatment involves stopping the offending drug

and a short course of systemic steroids may be helpful. Topical steroids and emollients should be applied. Antihistamines should be added to relieve pruritus.

Figure 1: Maculopapular rash due to amoxicillin



2. Erythroderma

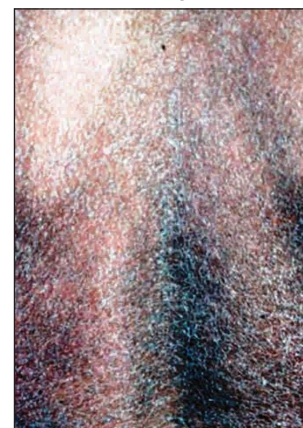
Erythroderma is the term applied to any inflammatory skin disease, which affects more than 90% of the body surface with erythema and scaling. Although it usually occurs as a complication of several inflammatory skin diseases, drugs are also a major cause. It may or may not follow exanthematic eruptions. Drug induced erythroderma usually starts days to weeks following ingestion of a drug, with widespread erythema followed by extensive exfoliation, hence the term exfoliative dermatitis is often used (Figure 2a and 2b).

In erythroderma normal skin barrier function is disrupted and life threatening complications may occur e.g. septicæmia, hypothermia,

Figure 2a: Erythroderma due to carbamazepine in an epileptic patient



Figure 2b: Close-up view, note marked erythema and scaling



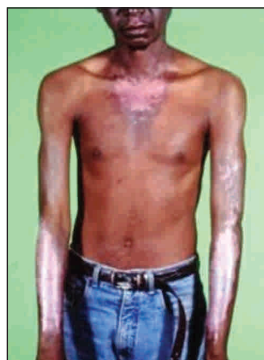
dehydration and electrolyte imbalances. Several drugs have been implicated in erythroderma, and these include antibiotics, anticonvulsants, antipsychotics and NSAIDs. Patients with erythroderma from whatever cause are better treated as in-patients. In drug induced erythroderma the offending drug must be stopped immediately. A short course of systemic steroids is administered to get the patient out of the acute crisis. Topical steroids and emollients should be applied. Antibiotics may be

necessary for secondary bacterial infections. Other supportive measures include maintenance of fluid and electrolyte balance as well as nutritional support.

3. Drug induced photosensitive dermatitis

This is a drug-light reaction, which causes eruptions on sun exposed areas of the body, thus the face, upper part of the chest, and extensor aspects of the arms. This reaction may be phototoxic or photo-allergic. Phototoxic reaction can be produced in almost all individuals given high dose of a drug and sufficient light irradiation. Photo-allergic reactions require a latent period during which sensitization occurs, and usually appear within 24 hours of re-exposure to drug and light in a sensitized individual. Drug induced photosensitive dermatitis may present as erythema, blistering, desquamation and residual hypo- or hyperpigmentation on sun exposed areas (Figure 3).

Figure 3: Photosensitive dermatitis, note the typical distribution on sun-exposed areas



These reactions can occur due to antibiotics, antiepileptics, antipsychotics, antihypertensives, NSAIDs and many other groups of drugs. (It is important to remember that HIV and connective tissue diseases are also major causes of photosensitivity and must always be excluded). Treatment: Substitute the offending drug with suitable alternative and topical steroids should be applied on affected areas. Sun protection may be necessary.

4. Fixed drug eruption

This presents as well circumscribed round to oval slatey-grey macules. They characteristically recur on the same sites each time the drug is administered, with each exposure, however the number of involved sites may increase.^{1,2,3} Lesions may occur on the trunk, limbs, genitalia, perianal and perioral areas (Figure 4). Although fixed drug eruption can be caused by many drugs, phenolphthalein found in laxatives is one of the commonest causes³, thus this condition is seen more frequently in people who take laxatives. The offending drug should be identified and stopped. Potent topical steroids should be applied, however hyperpigmentation may persist for longer periods despite adequate treatment.

Figure 4: Fixed drug eruption due to trimethoprim-sulfamethoxazole



5. Erythema multiforme

Erythema multiforme is another common form of cutaneous drug reaction. Typical lesions are called "target lesions".

These lesions are usually less than 3cm in diameter, rounded, and have three concentric zones; a central area of dusky erythema, a middle paler zone of oedema, and an outer ring of erythema with a well defined edge.^{4,5} (Figure 5) These lesions appear in successive crops. There may be few lesions or may be profuse. Classically the backs of the hands, palms, wrists, feet and extensor aspect of elbows are affected.

Patients who present with target lesions alone are diagnosed as erythema multiforme minor, whilst

Figure 5: Erythema multiforme minor due to penicillin (Pen VK)



target lesions plus involvement of at least two mucous membranes comprise erythema multiforme major or Stevens-Johnson syndrome (Figure 6). Steven-Johnson syndrome is a more severe form of erythema multiforme. The onset is usually sudden, although there may be a prodromal systemic illness of 1 – 13 days before the eruption appears. Numerous organs are affected. In one review of 81 cases, changes were found with the following frequency: mouth 100%, eyes 91%, skin 83%, male genitalia 57%, anal mucous membrane 5%, bronchitis 6%, pneumonitis 23%.⁴ The mouth and lips show characteristic haemorrhagic crusting.⁶

Figure 6: Child with Stevens-Johnson syndrome due to amoxicillin. Note mucosal involvement



Patients with Stevens-Johnson syndrome should ideally be admitted in hospital. Attention should be paid to maintenance of fluid and electrolyte

Figure 7a: Toxic epidermal necrolysis due to trimethoprim-sulfamethoxazole



Figure 7b: Toxic epidermal necrolysis due to ibuprofen



balance. Sepsis if any should be treated accordingly. The use of systemic steroids in Stevens-Johnson syndrome is controversial. Topical steroids and emollients can be applied. These patients often have oral mucosal involvement and therefore unable to feed, therefore nutritional support is important.

6. Toxic Epidermal Necrolysis

Toxic Epidermal Necrolysis (TEN) is a severe form of Stevens-Johnson syndrome associated with considerable morbidity and mortality.⁴

The condition presents within hours or days of medication administration with tenderness on the skin followed by widespread erythema. The epidermis becomes necrotic, full thickness splitting of skin with denudation occurs. (Figure 7a and 7b). Buccal, genital, nasal and ophthalmic mucous membranes are often involved. The clinical picture of TEN resembles that of thermal burns and causes of death are dehydration and sepsis. Healing of lesions occurs with scar formation. Ocular complications occur in 40 – 50% of survivors and include ectropion, entropion, synblepharon, corneal opacities and blindness. There is no specific drug treatment for this condition. Important measures include maintenance of fluid and electrolytes balance prevention and treatment of sepsis, and wound dressing. Patients with severe disease and extensive skin loss should be transferred to intensive care unit or to a burns unit, and subsequently managed as if they were suffering from thermal burns of the same degree.⁴

Systemic steroids are not helpful in TEN. Several groups have suggested that systemic steroids should not be used because they increase mortality due to sepsis.^{7,8,9} The use of intravenous immunoglobulins (IVIG) in the treatment of TEN was first suggested in 1998, and showed good results in some centres.^{10,11} Studies have shown that early use of IVIG in TEN results in rapid clinical improvement, shorter hospital stays and decreased mortality.^{10,11,12} Toxic epidermal necrolysis can occur due to antibiotics, anticonvulsants, NSAIDs, antifungals and many other drugs.^{10,11,12}

Recently a case of fatal toxic epidermal necrolysis due to lansoprazole was reported.¹³ In this report a patient who previously had erythema multiforme following intake of lansoprazole was later inadvertently prescribed the same drug. This time he had a fatal toxic epidermal necrolysis and died. This case illustrates the perils of rechallenge with a drug that has previously caused a

skin reaction. Furthermore, it highlights the need to communicate effectively about drug sensitivities, both to the patient and amongst clinicians. Medic alert bracelets must be mandatory to reduce the risk of inadvertent drug re-exposure. 🙋

See CPD Questionnaire, page 34

Conflict of interests:

None

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